Bioreactor design and optimization – a future perspective

Gernaey, Krist

Published in:
BIOTECH International

Publication date:
2011

Document Version
Publisher's PDF, also known as Version of record

Bioreactor design and optimisation – a future perspective

By Dr Krist V. Gernaey

Bioreactor design and optimisation are essential in translating the experience gained from lab or pilot scale experiments to efficient production processes in industrial scale bioreactors. This article gives a future perspective on bioreactor design and optimisation, where it is foreseen that technologies including mechanistic models, process simulation and advanced model analysis will play an increasingly important role.

One of the cornerstones in the establishment of a more sustainable future industrial production is the development of new and innovative bio-based manufacturing processes. Fermentation and biocatalysis are indeed finding increasing application for the manufacture of bulk chemicals, biofuels, fine chemicals, pharmaceuticals and agrochemicals. In practice, development of such bio-based manufacturing processes is often expensive and requires a tremendous experimental effort. First, during screening for new processes or applications, a large number of small-scale experiments is required to select the most suitable candidates. Second, when scaling up a process from lab to pilot to production scale, many time-consuming and expensive experiments are necessary to characterise those process conditions that yield the best performance.

Bioreactor design and optimisation are essential in translating the experience gained from lab or pilot scale experiments to efficient production processes in industrial scale bioreactors. It is foreseen that mechanistic models, process simulation and advanced model analysis, to name a few examples, will play an increasingly important role.

Mechanistic models for design purposes

Mechanistic process models are developed based on mass, heat and momentum balances, supplemented with appropriate mathematical formulations of mechanisms (e.g. kinetic expressions to reflect process dynamics). The resulting model typically consists of a number of ordinary differential equations (ODEs), and incorporates process stoichiometry and kinetics in a structured way. An important feature of mechanistic models is that they allow extrapolation of the data to understand the effects under untested conditions. Therefore, when available, those models can be used within process design and optimisation to exploit opportunities for process improvement which have not been tested experimentally [1].

When establishing (part of) a new factory, it is obvious that availability of a process model could be helpful. The required size of the reactor will, for example, depend strongly on the achievable conversion rates – rates that can be predicted with the mechanistic model. However, taking industrial fermentation as an example, the majority of the new products typically do not involve the design of a new plant dedicated to a single production process, but rather fitting the new reaction or strain and/or separation scheme into existing equipment. In this case, availability of a reliable process model, for example one developed on the basis of data generated during pilot-scale experimentation [2], enables *in silico* investigations of the process performance under different operation conditions before moving to full-scale production. In this way, introducing new products/strains in an existing factory is more efficient, since it can rely on the mechanistic model to evaluate the necessary trade-offs that will ultimately be needed in order to allow establishment of an efficient new production process within the constraints of the existing equipment.

Last but not least, a mechanistic model can be used in simulation studies aiming at the development of suitable process control strategies. Specifically for such applications, mechanistic models enable a realistic understanding of the effect of operating variables on product quality attributes.

Which forces drive development?

In recent years, the pharmaceutical industry has focused on establishing more efficient production processes in order to cut production costs.

The pharmaceutical industry was traditionally considered to be rather conservative, with fixed production processes, relying on extensive off-line lab analysis to guarantee product quality. However, the publication of the Process Analytical Technology (PAT) guidance [3] has been an important milestone, since this document made it clear that regulators were in favour of the establishment of more efficient production processes. A central statement there is "quality should not be tested into products, it should be built in by design". Focus in the PAT guidance is thus on acquiring process knowledge – including identification of the effect of critical process parameters (CPPs) on critical quality attributes (CQAs) of the final product – which is subsequently used to improve the process design and operation such that product quality can be increasingly guaranteed on the basis of a series of on-line measurements combined with suitable process control strategies ('real time release'), as illustrated in Figure 1.

Originally intended for the pharmaceutical industry, the PAT ideas have also spread to other industries, for example the food industry. In this respect, mechanistic models were suggested as a useful representation of available process knowledge, since the differential equations representing one or several unit operations in a production process inherently represent the input-output dynamics. This is precisely the type of information needed to pinpoint the causes of excessive variation of product quality or to select suitable actuators to counteract undesired variations in product quality. The model can be supplemented by a modeling toolbox including uncertainty and sensitivity analysis to assess the statistical quality (read as reliability) of the simulated scenarios [4].

Increasing model complexity

One trend is that increasingly complex models are developed as a consequence of availability of increased computational power. Model complexity is increased by including additional detail in a model, which will typically lead to improved accuracy and thereby also predictive power. Practically, including more detail can be achieved by replacing an unstructured with a structured model, or by transforming a non-segregated model into a segregated model. Also, computational fluid dynamics (CFD) can be used to model spatial distribution of reactants and hydrodynamics in large tanks, which is relevant to improving our understanding of the operation of large bioreactors. Such application of CFD modeling to fermentation and biocatalytic processes is expected to become increasingly common in the future. Industry is currently indeed focusing on optimising the exploitation of existing production capacity, and CFD could help achieve that goal. CFD can be taken a step further as well, and can be combined with models describing cellular metabolism [5].

Model complexity is also increased when combining models of several unit operations in a single plant-wide model, as for example illustrated by Dassau *et al.* [6]. The first advantage of a plant-wide model is that the interactions between the different unit operations can be considered, which is essential when comparing control strategies for a system *in silico*. Secondly, the most efficient bioprocess operation can only be achieved by focusing on the whole process rather than individual units. In this regard, the development of plant-wide models is usually carried out in a modular form, by connecting model blocks that represent individual unit operations. Notably, the development of a plant-wide model does not necessarily mean that all details in a production process need to be described with a mechanistic model. Indeed, a hybrid approach is often used, combining mechanistic models (i.e. mass and energy balances) with empirical models that describe parts of the process for which a detailed mechanistic model is not available [7].

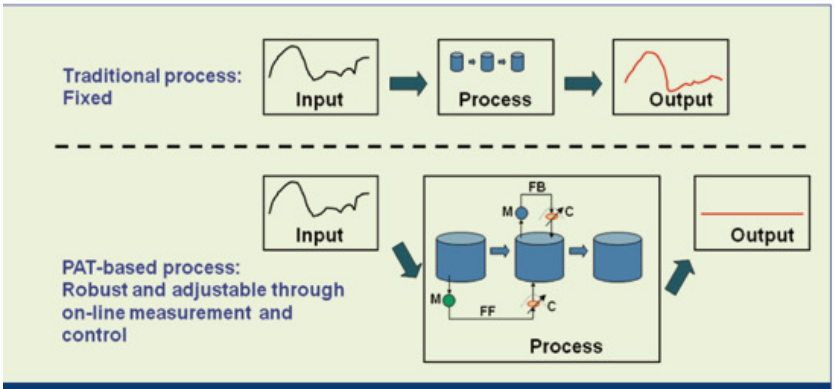

Figure 1. Comparison between a traditional 'fixed process' and the PAT-based approach where acquiring process knowledge leads to smart process design, resulting in a robust and adjustable production process (M = measurement; C = controller; FB = feedback; FF = feedforward)

Modeling cellular heterogeneity

Experimental methods for characterisation of distributed properties in a

population of cells, for example flow cytometry, are more and more accessible in research labs and industry. When such measured cellular heterogeneities within a single population (i.e. a 'pure' culture) of cells are to be included in a mechanistic model, model complexity increases as well. Population balance models (PBMs) form a modeling framework for describing such heterogeneities, and have for example been used to describe the age distribution in a population of yeast cells [8]. Future developments will involve the combination of spatial and population heterogeneity modeling by combining CFD with PBM or cell ensemble modeling. CFD has already been used to track individual cells in a yeast fermentation [5]. Such combined CFD-PBM models are considerably more complex to solve than a standard CFD model, thus leading to large calculation times. Nevertheless, the insight gained by implementing such detailed models is, in the long term, expected to translate into improved bioreactor design and operation.

Topology optimisation

There has recently been considerable interest in the development of microbioreactors (volume below 1 mL) that allow experimentation with microorganisms under well-controlled conditions [9]. When performing fermentation experiments at microscale, the increased design flexibility offered by the microfluidic systems enables a wide range of reactor configurations. In topology optimisation – a method originating from the structural mechanics field – a computer code is exploited to optimise the performance of a reactor on the basis of a suitable objective function. Topology optimisation has recently been applied to a theoretical microbioreactor example, where the spatial distribution of immobilised yeast cells in a microbioreactor was adjusted in order to optimise for maximal product flow out of the reactor [10], [Figure 2]. The topology optimisation method still needs experimental validation. However, if that could be achieved, the topology optimisation approach is potentially a powerful technique to support bioreactor design and optimisation.

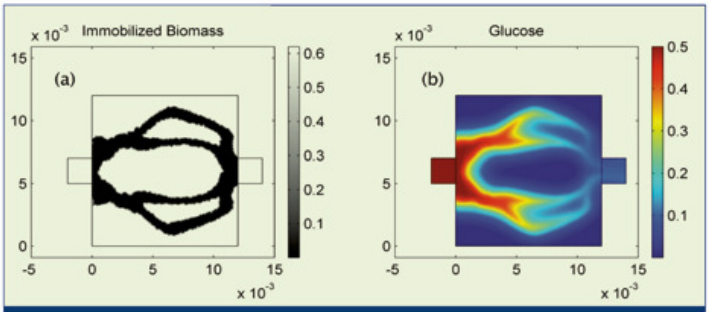

Figure 2. Topology optimisation [10]: Resulting structure and concentrations for a glucose inflow concentration of 0.5 $g.L^{-1}$. (Left) Distribution of biomass where white = cells and black = fluid, (Right) glucose concentration [$g.L^{-1}$],

References

1. Mathys RG, Schmid A, Witholt B. Integrated two-liquid phase bioconversion and product-recovery processes for the oxidation of alkanes: process design and economic evaluation. Biotechnol Bioeng 2009; 64: 459-477.
2. Albæk MO, Gernaey KV, Hansen MS, Stocks SM. Modeling enzyme production with Aspergillus oryzae in pilot scale vessels with different agitation, aeration and agitator types. Biotechnol. Bioeng. (submitted)
3. FDA (2004) Guidance for Industry. PAT - A framework for innovative pharmaceutical manufacturing and quality assurance, U.S. Food and Drug Administration, U.S. Department of Health and Human Services, Rockville 2004
4. Sin G, Gernaey KV and Eliasson AL. Good modelling practice (GMoP) for PAT applications: Propagation of input uncertainty and sensitivity analysis. Biotechnol Progr; 25: 1043-1053.
5. Lapin A, Muller D, Reus M. Dynamic behavior of microbial populations in stirred bioreactors simulated with Euler-Lagrange methods: traveling along the lifelines of single cells. Ind Eng Chem Res 2004; 43: 4647-4656.
6. Dassau E, Zadok I, Lewin DR. Combining six-sigma with integrated design and control for yield enhancement in bioprocessing. Ind Eng Chem Res 2006; 45: 8299-8309.
7. González-Sáiz JM, Garrido-Vidal D, Pizarro C. Modelling the industrial production of vinegar in aerated-stirred fermentors in terms of process variables. J Food Eng 2009; 91: 183-196.
8. Zamamiri AM, Zhang Y, Henson MA, Hjortsø MA. Dynamics analysis of an age distribution model of oscillating yeast cultures. Chem Eng Sci 2002; 57: 2169-2181.
9. Schäpper D, Zainal Alam MNH, Szita N, Eliasson Lantz A, Gernaey KV. Application of microbioreactors in fermentation process development: a review. Anal Bioanal Chem 2009; 395: 679-695.
10. Schäpper D, Lencastre Fernandes R, Elisasson Lantz A, Okkels F, Bruus H, Gernaey KV. Topology optimized microreactors. Biotechnol Bioeng (2011); 108; 786-796.

The author

Dr Krist V. Gernaey
Centre for Process Engineering and Technology
Department of Chemical and Biochemical Engineering
Technical University of Denmark
DK-2800 Lyngby
Denmark
e-mail: kvg@kt.dtu.dk